Treatment policy and hypothetical strategies for intercurrent events in chronic pain and Parkinson's disease

4th EFSPI Regulatory Statistics meeting
23/24 September 2019
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Introduction

- Two Case studies
  - Chronic pain
  - Parkinson’s disease
- Neuroscience Biostatistics Community SIG – working group on estimands
- Estimands combining differing handling strategies for different categories of intercurrent events (ICEs), i.e.
  - Treatment policy
  - Hypothetical
- Based on *draft* ICH E9 (R1)

some study design and drug characteristics were somewhat contrived to avoid implications for products of the sponsor, but key features were preserved

Case Study 1 in Chronic Pain

Georg Kralidis

Background

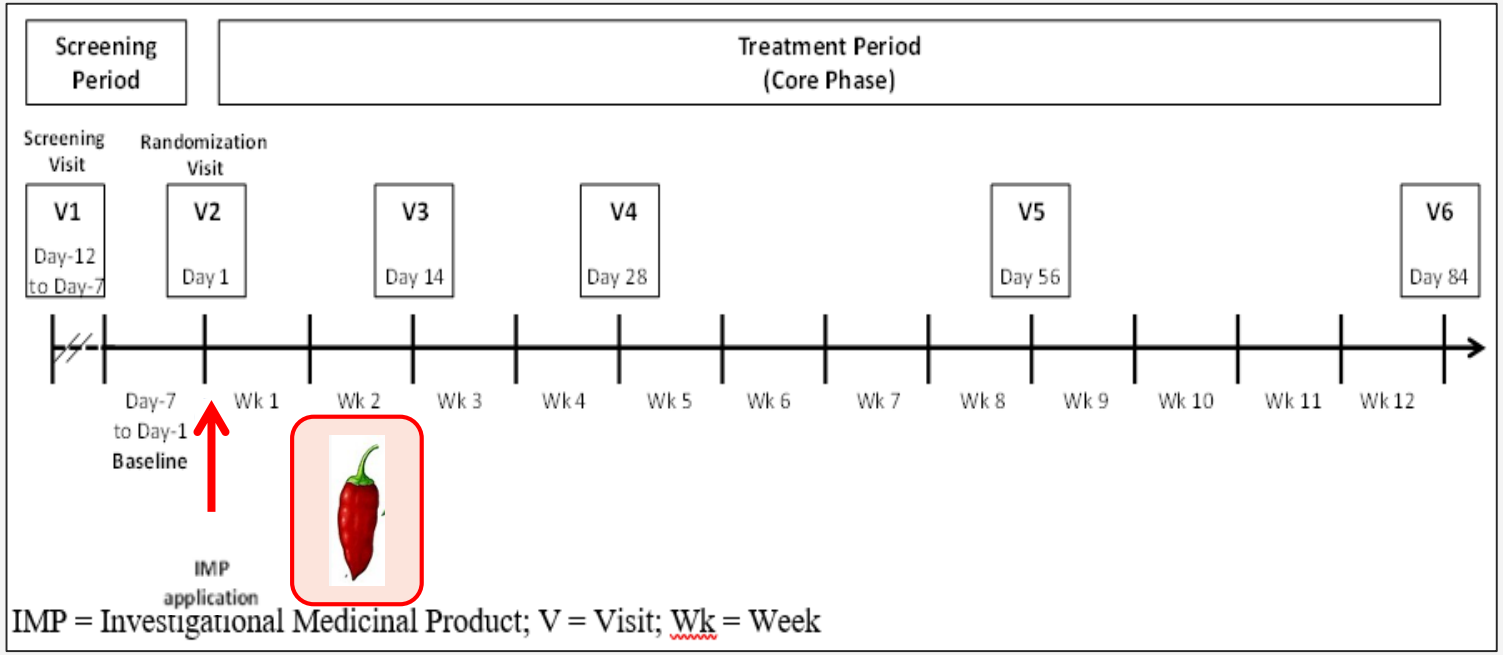
Case Study in chronic Neuropathic Pain (cNP)

Pain is a major health problem that substantially reduces quality of life. The indication pain is very heterogeneous, there are several types of pain, intensity levels, duration (acute, chronic)

A **cNP** indication: Pain occurs in a defined localized area of the body surface and can be treated by dermal patches.

Topically applied capsaicin induces reversible dermo-epidermal denervation and depletion of capsaicin sensitive nociceptors

Typical confirmatory capsaicin trial in chronic pain



Administration: **single application at baseline visit**

Trial objective, Effect of Interest

Case Study in chronic Neuropathic Pain (cNP)

Aim of trial: Satisfy regulatory requests for marketing authorization for indication of interest

- Population consists of subjects with moderate to severe cNP
- Chronic indication: three month effect is accepted as surrogate marker for even longer lasting effect:
  Endpoint: relative change from baseline to Week 12 in the 24-hr average pain intensity
- Superiority over placebo using difference in group means

Treatment regimen (Ratitch et al 2019, Mallinckrodt et al 2019) / Treatment strategy (Scharfenstein 2019)

- IMP: 30 minutes topical application of patch at painful affected area at baseline visit
- List of accepted adjuvant analgesics (no opioids) for short term use

Effect of interest :

- causal relationship between the treatment regimen of interest and effect
  [and not the causal relationship between act of randomization and effect]
- ICEs related to flexibility within treatment regimen: treatment policy strategy
- ICEs related to non-adherence to treatment regimen: hypothetical strategy
  [what would have happened if ICE did not occur]

List of plausible / relevant Intercurrent Events (ICE)

Case Study in chronic Neuropathic Pain (cNP)

ICE	Adherence
Start of intake of forbidden concomitant medication as opioids	Non-Adherence
Start of intake of allowed concomitant medication	Adherence

List of plausible / relevant Intercurrent Events (ICE)

Case Study in chronic Neuropathic Pain (cNP)

ICE	Adherence	Handling
Start of intake of forbidden concomitant medication as opioids	Non-Adherence	observed assessments after the ICE are replaced (hypothetical strategy to estimate outcome if all adhered)
Start of intake of allowed concomitant medication	Adherence	treatment policy strategy

List of plausible / relevant Intercurrent Events (ICE)

Case Study in chronic Neuropathic Pain (cNP)

ICE	Adherence	Handling
Start of intake of forbidden concomitant medication as opioids	Non-Adherence	observed assessments after the ICE are replaced (hypothetical strategy to estimate outcome if all adhered)
Start of intake of allowed concomitant medication	Adherence	treatment policy strategy
Discontinuation of treatment (interrupted patch application)	Non-Adherence	treatment policy strategy
Discontinuation of trial	(Adherence)	Unobserved assessments imputed (hypothetical strategy to estimate outcome if all adhered)
Monitoring for unexpected ICEs	…	…

Analysis method, missing data handling

Case Study in chronic Neuropathic Pain (cNP)

Primary Analysis:

- mixed-effects model for repeated measures (MMRM) correcting for country/region, gender, week, treatment-by-week interaction and baseline pain intensity

- Missing data handling:

  In treatment of symptoms such as pain, early discontinuation is usually considered a negative outcome (i.e. assuming that treatment effect disappears after stop of intake)

  not the case for capsaicin due to its long-lasting PD effect:
  not observed observations after trial discontinuation or excluded assessments after intake of prohibited medication handled as MAR

not addressed:

- Sensitivity analysis Tipping point (Permutt, 2016), trimmed means (Permutt & Li, 2017)
- Trial discontinuation: reason dependent handling?
- Secondary Efficacy and Safety estimands
- Blinded extension phase

Case study 2: Estimands in early Parkinson's disease

Marcel Wolbers, on behalf of the Early PD Estimand Working Group

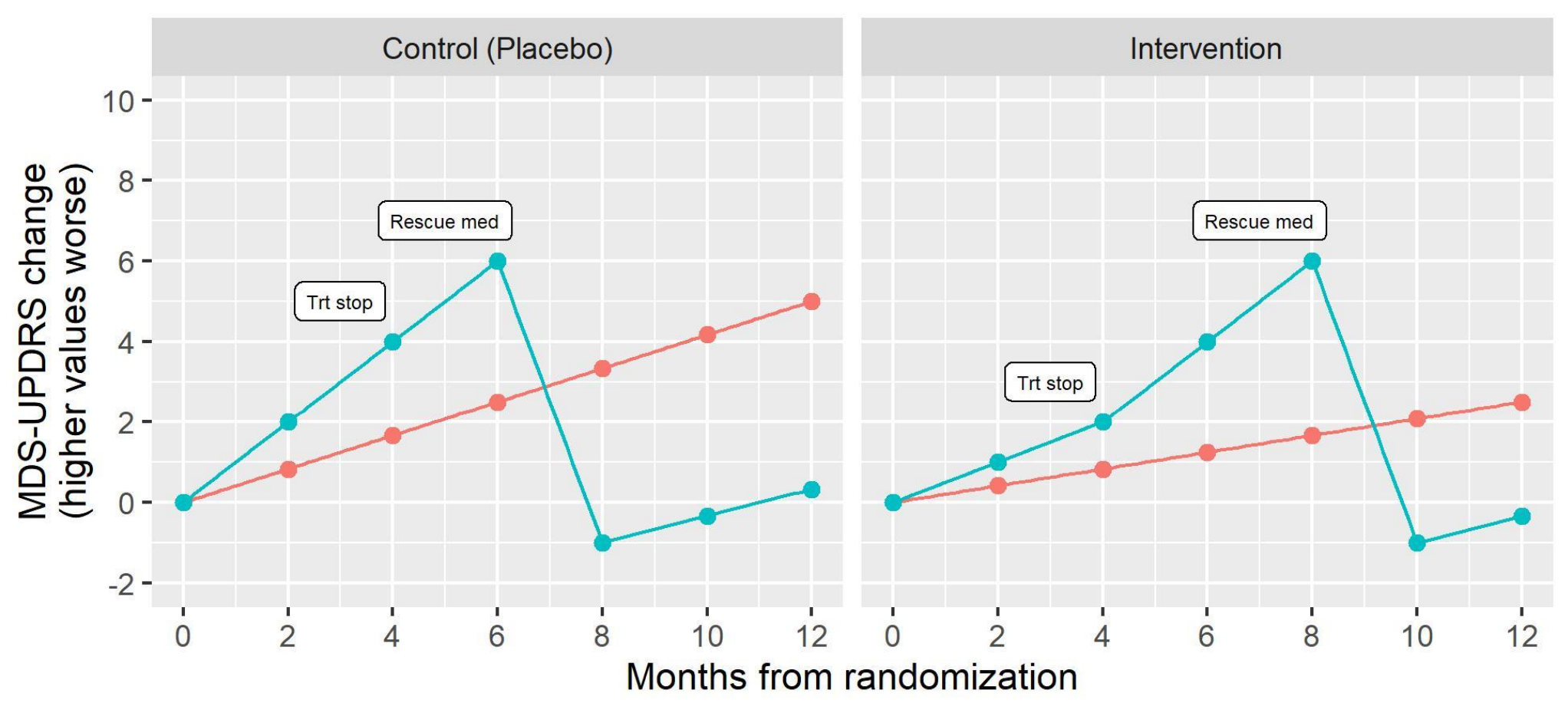
(Markus Abt, Hans Ulrich Burger, Christopher Coffey, Beki Finch, Man Jin, Mette Krog Josiassen, Ting Li, Romeo Maciuca, Sofia Mosesova, Weining Robieson, Marcel Wolbers)

Parkinson’s disease (PD)

- ~7 Mio people affected globally, expected to increase
- PD cannot be prevented, slowed or cured as of today
- Highly effective *symptomatic* treatments are available (e.g. dopaminergic treatments)
  - Initiated within 12 mo in ~30% of subjects in early PD
  - Initiation depends on current MDS-UPDRS score but is highly variable
- Most commonly used symptom scale: MDS-UPDRS score (total or part III (motor))

→ Estimand of choice for an MDS-UPDRS-based endpoint in the development of a potentially *disease-modifying* treatment in early PD?

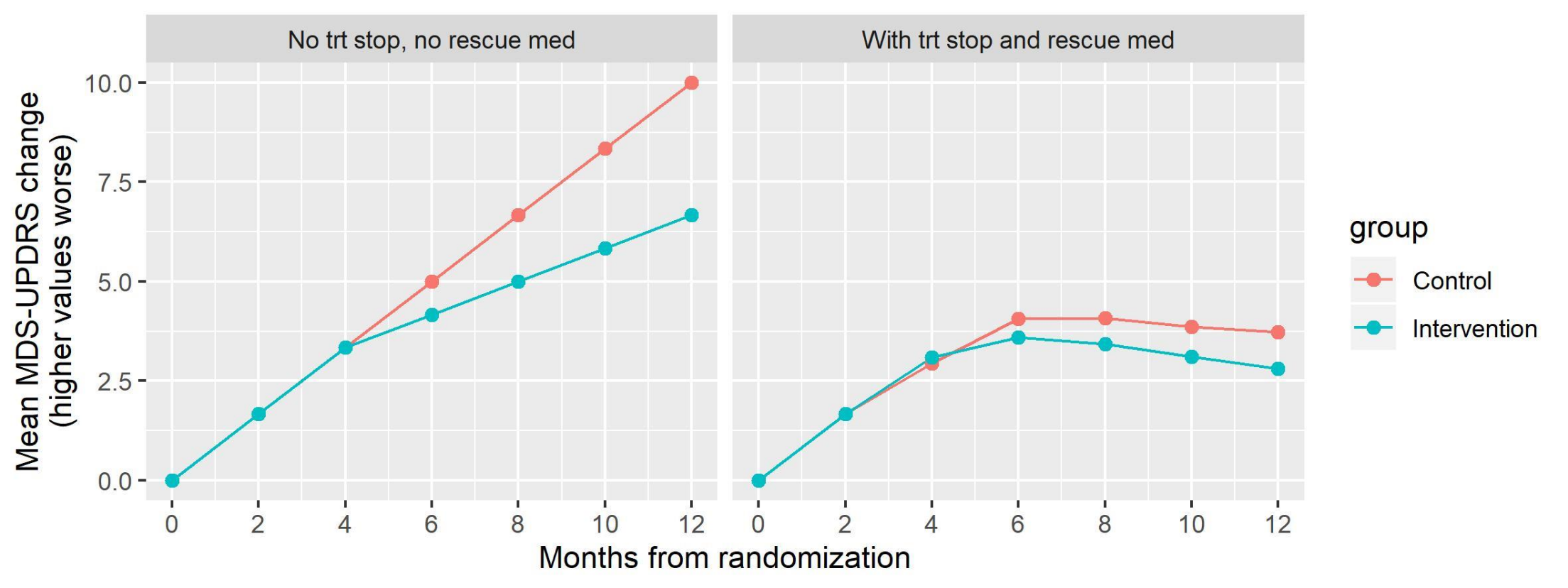
Stylized individual MDS-UPDRS trajectories



Trajectories for two subjects per arm are shown

Rescue medication → Subjects with «worse outcome» may have better/lower MDS-UPDRS scores at end of study

Stylized population MDS-UPDRS trajectories*



Effect of rescue medication on treatment policy estimand: Reduced treatment effect and increased variance

*Simulated using parameters inspired by analyis of PPMI cohort

Proposed estimand

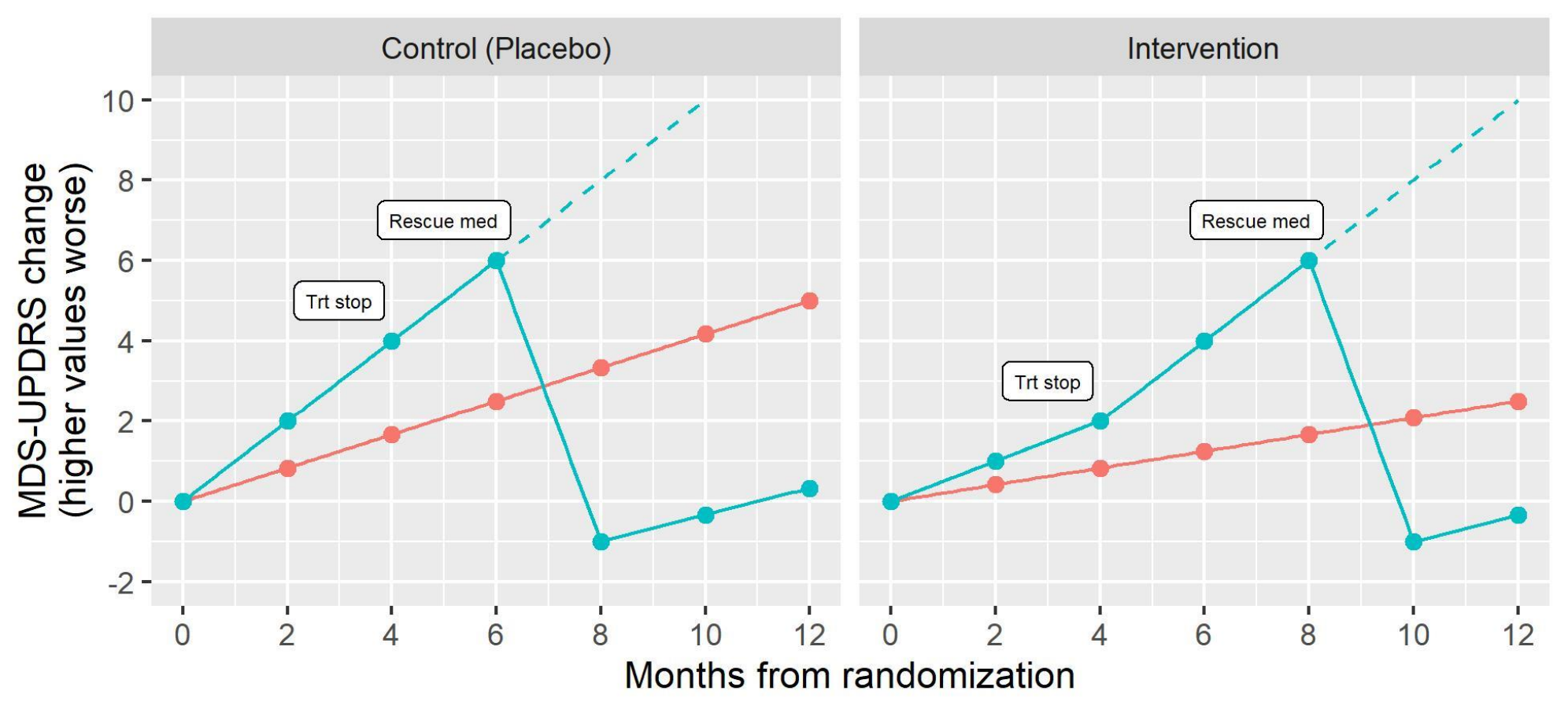
Proposal: Mean change of MDS-UPDRS score from baseline to week 52 regardless of discontinuation of study drug but excluding effects of rescue medication (dopaminergic treatment)

”Treatment policy ” for study drug discontinuation

”Hypothetical” for rescue medication

Data collection: Assume continuation of MDS-UPDRS assessments after discontinuation of study drug

Stylized individual MDS-UPDRS trajectories



Trajectories for two subjects per arm are shown

Dashed lines display unobserved trajectories in a hypothetical world without rescue medication

Proposed estimator

Intercurrent event (ICE)	Treatment arm	Analysis
Withdrawal from treatment	Control	- Use assessments post withdrawal (if available) - If not, impute based on control arm
Start of rescue medication	Control	- Remove assesssments after rescue (if available) - Impute based on control arm
Withdrawal from treatment	New treatment	- Use assessments post withdrawal (if available) - If not, impute based on control arm
Start of rescue medication	New treatment	- Remove assesssments after rescue (if available) - Impute based on control arm*

*Assumption: Rescue medication initiated shortly after study drug withdrawal

Conclusions

Benefits of ICH E9 addendum

- Helps clarifying which ‚effect' we are aiming to estimate
- Provides framework for detailed description of handling of ICEs
- Different strategies for different types of ICE foreseen

Case studies

- Chronic pain example
  - ICE strategy chosen to allow investigation of causal effect of treatment regimen
  - MAR assumption justified via drug properties
- Parkinson's disease
  - Pure treatment policy strategy infeasible in view of highly effective but symptomatic rescue treatments

References

- Draft ICH E9 (R1), 2017 https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf

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- Scharfstein D. A constructive critique of the *draft* ICH E9 Addendum. Clinical Trials 2019; 16 (4): 375-380
- Ratitch B, Bell J, Mallinckrodt C, et al. Choosing Estimands in Clinical Trials: Putting the ICH E9(R1) Into Practice. Ther Innov Regul Sci 2019; doi: 10.1177/216847901983827. [Epub ahead of print]
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Thank you!